7 Stomach and Duodenum

Stomach

The stomach is composed of several anatomic zones. Moving proximal to distal, like a piece of food, you pass (1) the gastroesophageal junction, (2) the cardia, (3) the fundus or body, (4) the antrum, and (5) the pylorus (Table 7.1 and Figure 7.1). For the pathologist, there are essentially two types of mucosa in the stomach (Figure 7.2), antral and oxyntic, as cardiac mucosa looks very similar to antrum. The entire stomach epithelium is composed of pits (invaginations from the surface) and glands (deep to the pits). The surface and pits are lined by columnar mucinous epithelium (sometimes called *foveolar type*) which stains bright pink with PAS/AB. The regions of the stomach are divided by the type of underlying glands:

- *Antral* mucosa (found in the antrum): The glands are loosely packed, mucinous, and occupy about half of the epithelial thickness. Cardiac mucosa looks very similar.
- *Oxyntic* mucosa (found in the fundus or body): The glands are tightly packed, contain granular parietal (pink, acid-secreting) and chief (purple, enzyme-secreting) cells, and occupy three fourths of the mucosal thickness.
- *Transitional* mucosa: Features of both antral and oxyntic are present. Transitional mucosa represents the overlap zone.

It is important to note what kind of epithelium is present in the biopsy tissue so that the endoscopists can correlate with what they saw. Also, there are certain processes that differentially affect mucosal types; clarifying the type of epithelium involved may change the differential.

Endocrine cells occur singly in the glands. In the body, they are mainly enterochromaffin-like cells, while in the antrum they are mixed gastrin, enterochromaffin, and somatostatin. A chromogranin stain highlights all endocrine cells. A gastrin stain should be positive only in the antrum.

The Approach to the Biopsy

Survey the glandular epithelium at low power:

- The first thing to notice is what kind of mucosa you have and whether it correlates with what the endoscopist told you. Then decide on the color of the biopsy specimen. A healthy stomach is a pretty pale pink, overall. If your general impression is blue, this probably indicates inflammation in the stroma, such as in gastritis (Figure 7.3). If your impression is that of a pink stroma with unusually dark and distinct glands, you may be looking at chemical gastritis.
- Goblet cells are usually visible from low power, especially on the PAS/alcian blue (AB) stain (as indigo-blue, bulbous cells), and indicate intestinal metaplasia, a marker of chronic

TABLE 7.1. Anatomic zones of the stomach.

	Esophagus	Cardia	Fundus	Antrum	Pylorus
Histology	Squamous	Cardiac (antral)	Oxyntic	Antral	Antral to duodenal
Endocrine cells	None		Enterochromaffin-like	Gastrin, somatostatin, enterochromaffin	
Common pathology	Reflux esophagitis	Reflux carditis *Helicobacter pylori*	Autoimmune gastritis	*H. pylori* gastritis Chemical gastritis	Chemical gastritis

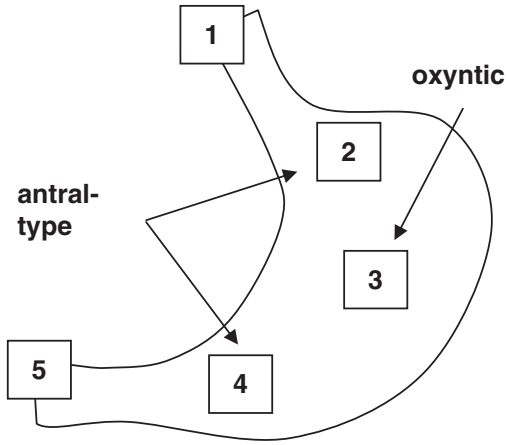

FIGURE 7.1. Localization of anatomic regions within the stomach: (1) the gastroesophageal junction, (2) the cardia, (3) the fundus, (4) the antrum, and (5) the pylorus. Antral-type (mucinous) mucosa is seen in the cardia and the antrum.

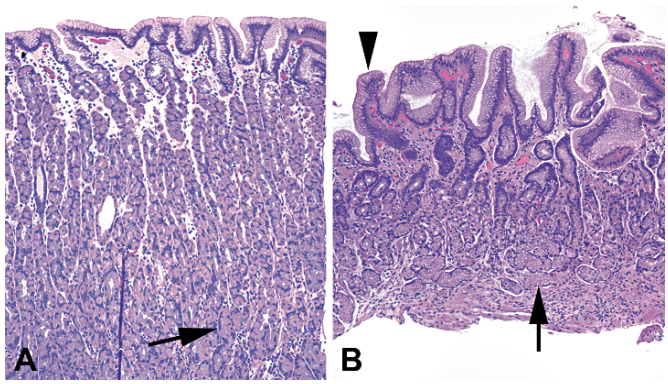

FIGURE 7.2. Antral and oxyntic mucosa. **(A)** Oxyntic mucosa is relatively thick, with most of the mucosa occupied by secretory cells (arrow), the parietal and chief cells. The surface is composed of mucinous foveolar epithelium. **(B)** Antral mucosa is thinner, and the glands are mucinous instead of secretory (arrow). However, the surface is still composed of foveolar epithelium (arrowhead).

irritation in the stomach. Remember that true goblet cells are usually interspersed among nonmucinous pink cells (absorptive). A row of back-to-back tall mucinous cells, even if blue on PAS/AB, is unlikely to be actual intestinal metaplasia.

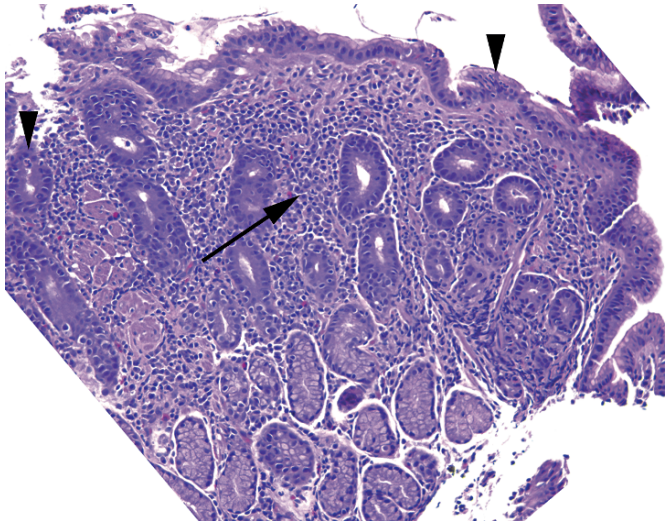

FIGURE 7.3. *Helicobacter pylori* gastritis, antrum. In this disease, the low-power impression is that of a "blue" biopsy due to the dense inflammatory infiltrate in the lamina propria (arrow). There are lymphocytes, plasma cells, and neutrophils. Neutrophils in the glandular or surface epithelium (arrowheads) indicate an active component to this gastritis. *Helicobacter pylori* organisms are pictured in Chapter 3.

- Areas of exudate, neutrophils, debris, and ragged-looking glands indicate an erosion or ulcer. Ulcers are discussed in more detail later.

On higher power, assess the inflammation:

- A few *lymphocytes, plasma cells*, and *eosinophils* are okay in the stomach, especially in the antrum, where there is more space between glands. However, back-to-back lymphocytes and plasma cells pushing aside or crowding the glands indicate a chronic gastritis.
- The presence of neutrophils in the stomach indicates *activity* and is not called *acute* as in other organs. If you have only mononuclear cells, you have an inactive chronic gastritis, but if there are any neutrophils embedded in the surface or glandular epithelium, you have an active chronic gastritis.
- Neutrophils, chronic gastritis, and lymphoid follicles are all associated with *Helicobacter pylori* infection. The tiny rods are visible on hematoxylin and eosin stain (see Chapter 3) but are better seen on Diff-Quik or Giemsa. They should be visible at 40× as tiny discrete seagull-shaped rods in the pit lumens or on the surface, mainly in the antrum, unless there is intestinal metaplasia, a hostile mucosa for these bugs. If you have no significant inflammation, do not work too hard looking for *H. pylori*.
- How many lymphocytes does it take to diagnose *lymphoma*? Lymphoma in the stomach often arises from mucosa-associated lymphoid tissue (MALT), is of marginal zone phenotype, and is a result of chronic *H. pylori* infection. You should see sheets of monocytoid B cells (fried egg–like) and lymphoepithelial lesions (lymphocytes embedded in epithelium) before considering this diagnosis.

Foveolar Hyperplasia

Especially in the antrum, the stomach is vulnerable to bile reflux. Bile and other sources of chemical irritation, such as nonsteroidal anti-inflammatory drugs, cause a process called *foveolar hyperplasia*. The surface mucin cells proliferate, giving the surface a papillary appearance and the pits a corkscrew profile. The mucinous cells lose mucin, and the cytoplasm becomes more dark or opaque; the nuclei also may become hyperchromatic, adding to the dark look (Figure 7.4). Smooth muscle fibers proliferate and can be seen stranding up between

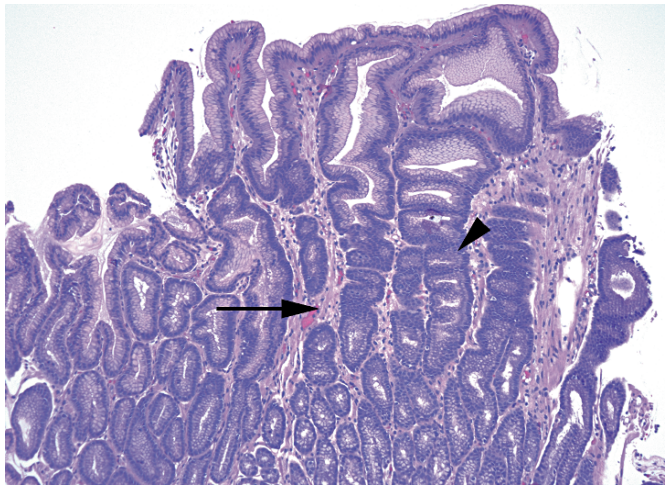

Figure 7.4. Chemical gastritis, antrum. In chemical gastritis, the lamina propria shows very little inflammation, unlike in *Helicobacter pylori* gastritis. The lamina propria is pale and sometimes edematous such that the dark reactive nuclei of the glands stand out sharply in contrast. The corkscrew profile of the hyperplastic glands is a second classic feature (arrowhead), as is the presence of thin strands of smooth muscle between the glands (arrow).

the pits. Inflammation in the stroma is not a prominent feature, so the lamina propria is often fairly pale, even edematous. This appearance is called *chemical gastritis*, and it is very common.

Atrophy

The loss of glands in the stomach, in any region, is called *atrophy*. Atrophy can be difficult to assess on any given biopsy specimen, as badly oriented sections, a healing ulcer, or dense inflammation can all lead to the appearance of loss of glands. Regardless of the cause, true atrophy, as an end-stage response to severe chronic damage, should be accompanied by intestinal metaplasia and inflammation (Figure 7.5). The two principal types of atrophy are the following:

- *Helicobacter pylori* gastritis (formerly known as *environmental metaplastic atrophic gastritis*) is secondary to *H. pylori* infection, primarily affects the antrum, and involves loss of glands in the setting of active chronic gastritis and intestinal metaplasia. You may also see lymphoid follicles and pit abscesses (pits full of neutrophils).
- Autoimmune gastritis (formerly known as *autoimmune metaplastic atrophic gastritis*), a result of the autoimmune destruction of the parietal cells in the fundus, shows loss of fundic glands in the setting of chronic inflammation and intestinal metaplasia. It is associated with a compensatory antral G-cell hyperplasia and hypergastrinemia. The hyperplasia may even progress to microcarcinoids or tumorlets. In autoimmune gastritis, you should not see activity or lymphoid follicles.

In severe autoimmune gastritis, the body of the stomach comes to resemble the antrum due to the atrophy of the secretory glands. It can therefore be difficult to decide if it is antrum or truly atrophic oxyntic mucosa. A gastrin stain, which will stain only true antrum, will help.

Lymphoma

Although diffuse large B-cell lymphomas are the most common lymphoma in the stomach, and should be considered if you see sheets of very ugly cells, differentiating them from normal inflammation is not usually a problem. Low-grade lymphomas, however, are tricky, especially given that most arise in the setting of chronic *H. pylori* gastritis. As mentioned earlier, you may see a background of lymphoepithelial lesions, which are collections of

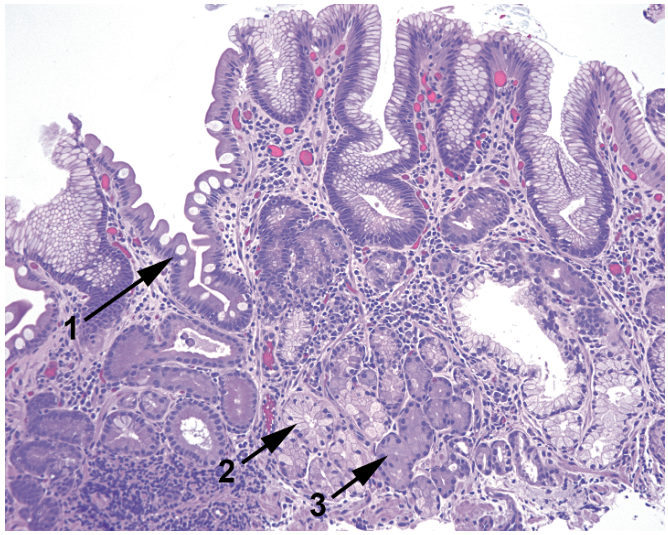

Figure 7.5. Autoimmune gastritis. This fundic biopsy specimen shows several features of atrophy. The surface shows goblet cells, which are indicative of intestinal metaplasia (1); deep to this there is inflammation and replacement of the secretory glands by mucinous, antral-type glands (2). Some residual oxyntic cells are also visible (3).

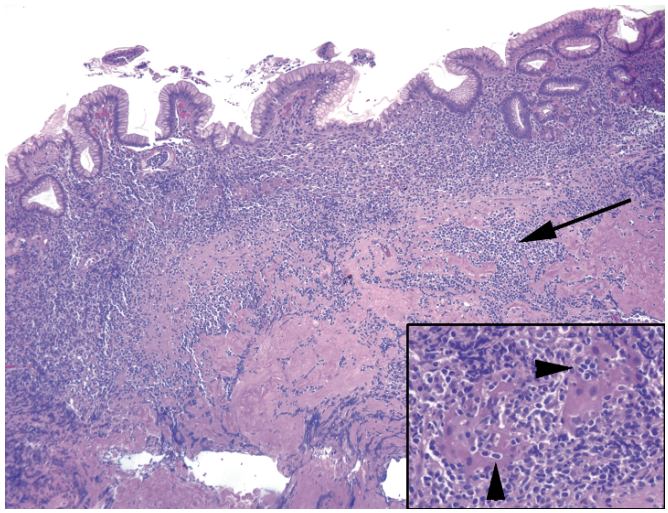

Figure 7.6. Mucosa-associated lymphoid tissue lymphoma. There are sheets of lymphocytes under the epithelium and dissecting into the muscularis mucosa (arrow). **Inset**: Lymphoepithelial lesions are typical, in which residual glands (seen here as little more than islands of pink cytoplasm) are infiltrated and destroyed by lymphocytes (arrowheads).

lymphocytes that appear to be eating glands (Figure 7.6), lymphoid follicles, and neoplastic plasma cells. Mucosa-associated lymphoid tissue lymphoma is usually of the marginal zone type, which is monocytoid in appearance (small round nuclei surrounded by a halo of clear cytoplasm).

Immunostains are often used to establish the diagnosis. In a MALT lymphoma, the majority of the cells should be B cells ($CD20^+$) that also stain for CD43. Normal T cells may also stain for CD43, so you must mentally subtract out the background T cells (shown by CD3 stain). Helpfully, in chronic gastritis, most of the lymphocytes are T cells.

Ulcers

An ulcer is a full-thickness defect of the epithelium down to muscularis mucosa (an erosion is more superficial). It is accompanied by fibrinopurulent exudate and/or granulation tissue, plus reparative glands. Search the periphery for the reason for the ulcer, including *H. pylori*, chemical gastritis, and adjacent cancer. Reparative glands appear as small, angulated glands with little mucin, and the lamina propria around them may be fibrotic. This can be difficult to distinguish from invasive carcinoma. However, reparative glands should have small or reactive nuclei and should have an overall streaming parallel arrangement, as they all want to orient to the surface (Figure 7.7).

Polyps

A reasonable differential for a polypoid structure in the stomach includes the following:

- Fundic gland polyps: Fundic gland polyps look like oxyntic mucosa but with cystically dilated glands (Figure 7.8). They are common in older people. Multiple polyps occur in familial adenomatous polyposis.
- Hyperplastic polyps: Polyps are hyperplastic, elongated, or cystic foveolar pits with mild inflammation (Figure 7.9). They are usually associated with background gastritis.
- Adenomas: These are neoplastic and dysplastic nodules that can be either gastric type or intestinal type. The gastric type is not associated with malignancy, but the intestinal type can be, such as a tubular adenoma.

Dysplasia Versus Carcinoma

Dysplasia in the stomach is assessed similarly to dysplasia in Barrett's esophagus (see Chapter 6). As in Barrett's esophagus, intestinal metaplasia is an abnormal finding but by itself is not dysplasia. Dysplasia in gastric mucosa initially begins to look like a tubular adenoma of the colon (it gets blue). The nuclei show increased hyperchromatism and pleomorphism, high nuclear/cytoplasmic ratio, loss of mucin vacuoles, crowding and pseudostratification, and loss of polarity. *High-grade dysplasia* tends to be called when invasive carcinoma is suspected but

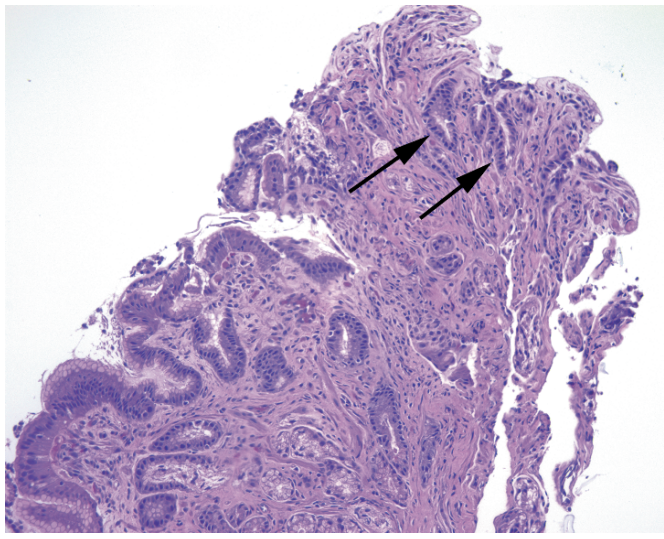

Figure 7.7. Reparative changes next to an ulcer. The tip of this fragment has a collection of poorly formed glands with an infiltrative look and minimal cytoplasm, giving the appearance of a high nuclear/cytoplasmic ratio (arrows). However, the nuclei are of about the same size and shape as the rest of the gastric glands, and these small glands stream in parallel toward the surface, consistent with regenerative or reparative glands.

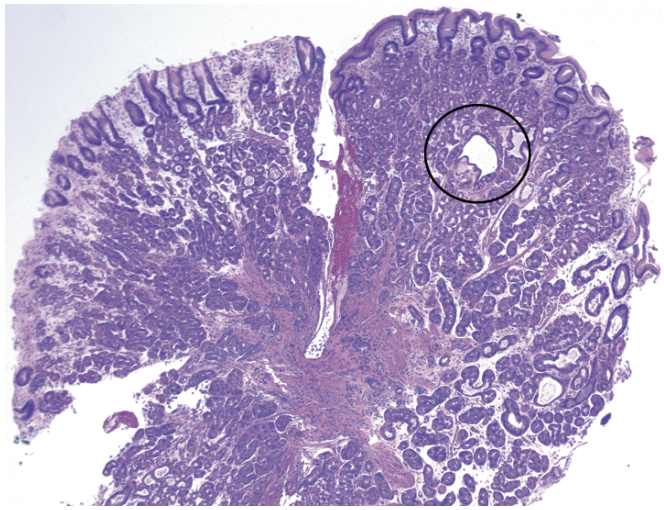

Figure 7.8. Fundic gland polyp. This polypoid fragment shows oxyntic- or fundic-type glands, with occasional dilated glands (circle).

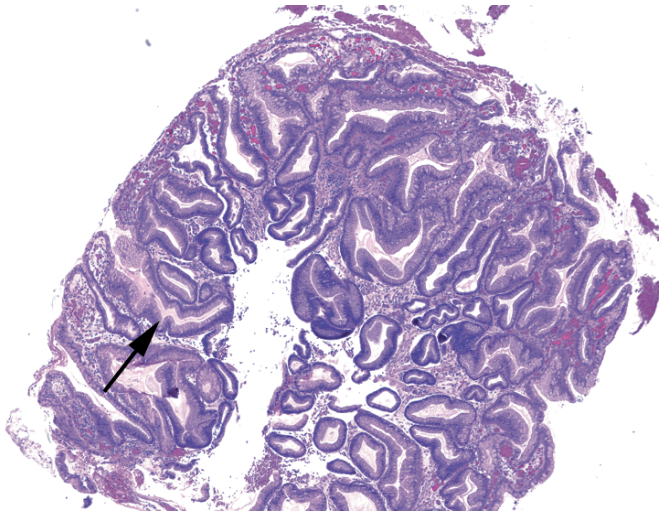

Figure 7.9. Hyperplastic polyp. This polyp is reminiscent of chemical gastritis, with corkscrew glands (arrow) and hyperplastic foveolar epithelium. Inflammation and intestinal metaplasia may be present.

cannot be proven. *Carcinoma in situ* is not used in this situation; think of high-grade dysplasia as synonymous.

Invasive adenocarcinoma comes in two types in the stomach: intestinal type (which looks like colon cancer, hence the name) and diffuse. The intestinal type is fairly easy to spot; it is usually associated with atrophy and intestinal metaplasia. The diffuse type is the poorly differentiated, often signet-ring, infiltrative cancer that can creep through the entire stomach and cause linitus plastica. Signet-ring cell carcinoma gets its name from the single vacuolated cells with displaced and indented nuclei (Figure 7.10). They can look like foamy macrophages, and they can blend almost imperceptibly into the stroma. Every stomach biopsy specimen should get a once-over at high power, such as 20×, to scan the lamina propria for signet rings. When they are there, often you will see the first one and then realize there are hundreds of them.

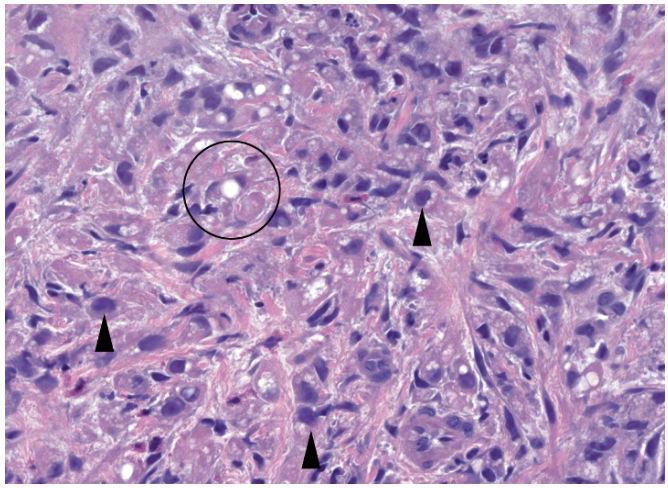

Figure 7.10. Signet-ring cell carcinoma. At low power, this sneaky tumor may be visible as little more than a slightly busy or cellular lamina propria. At high power, you can see individual signet-ring cells with single large mucin vacuoles (circle), plus other single infiltrating cells with large hyperchromatic nuclei (arrowheads). The signet-ring cells differ from fat cells by having large dark nuclei that protrude up from the surface of the central vacuole.

The Submucosa

The submucosa is not always included in a biopsy specimen. It lies below the thin muscularis mucosa. However, there are some things that are more often found in the submucosa, including the following:

- Heterotopic pancreas is a nodule of well-developed pancreas.
- Gastrointestinal stromal tumors, which arise from the interstitial cells of Cajal, are spindle-cell neoplasms that should stain for c-kit (CD117).
- Leiomyomas arise from smooth muscle cells. Leiomyoma is the second entity in the differential for are spindle-cell neoplasm. It stains for smooth muscle markers but not c-kit.
- Carcinoids may be mucosal or submucosal; they have similar morphology to carcinoids elsewhere. Carcinoids may be sporadic, they may arise in multinodular form in response to autoimmune gastritis, or they may be associated with multiple endocrine neoplasia (MEN) syndromes.

Duodenum

Duodenum is included here as duodenal tissue often accompanies stomach tissue in biopsy specimens, and the pathology in some cases is continuous. A duodenal biopsy may be performed because of combined gastritis and duodenitis, with or without peptic ulcer disease; to investigate suspected malabsorption syndromes, such as celiac disease; or to diagnose a mass lesion.

Normal duodenal mucosa is characterized by narrow villi that project above the mucosal surface. The epithelium is intestinal type, which means goblet cells are interspersed among the absorptive cells. Lymphocytes, plasma cells, and eosinophils are normal inhabitants of the lamina propria. A few intraepithelial lymphocytes may be seen, although they should not be found at the tips of the villi. Under the muscularis mucosa are collections of mucous glands called Brunner's glands, which stain bright pink on PAS/AB.

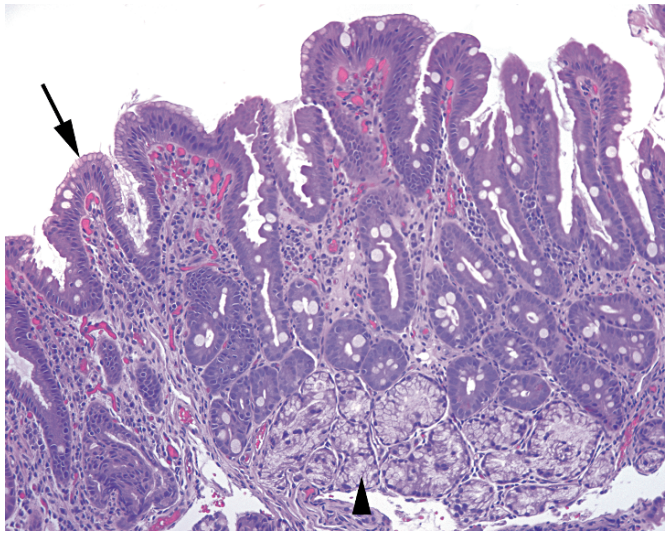

Figure 7.11. Chronic peptic duodenitis. At the surface, there is a subtle metaplastic change (arrow), where the normal absorptive and goblet cells are replaced by mucinous, foveolar-type cells, similar to those seen in antrum. There is increased chronic inflammation in the lamina propria and Brunner's gland hyperplasia (arrowhead).

Chronic Peptic Duodenitis

In severe gastritis, the inflammation and increased acid secretion may spill into the duodenum. In response to the lowered pH, the duodenum may "turn itself into stomach" or acquire gastric-type metaplasia. This shows up as metaplastic mucinous cells lining the villi (Figure 7.11) and is very obvious on PAS/AB stain because of the pink color of the gastric-type mucin. Other changes include Brunner's gland hyperplasia, which is a mucosal (as opposed to a submucosal) proliferation of glands, and increased inflammation in the lamina propria. Advanced cases may ulcerate.

Celiac Disease

Although celiac disease, or sprue, is not very common, requests to rule it out are fairly frequent. The classic picture of advanced celiac disease is that of a completely flattened mucosa, with total loss of villi, such that the duodenum mimics colon (Figure 7.12). The absorptive epithelium loses its brush border and flattens into a low cuboidal layer, hence the resulting malabsorption. However, more subtle findings include villous blunting, or loss of villous height, and prominent intraepithelial lymphocytes at the tips of the remaining villi. Evaluating villous blunting can be difficult in a poorly oriented or mangled mucosal fragment; also keep in mind that the differential for villous atrophy is long and is only diagnostic of celiac disease if the serology and clinical picture agrees.

Infections of the duodenum include those caused by *H. pylori*, which can rarely occur in the setting of gastric mucin cell metaplasia, and giardiasis. *Giardia* is very sneaky, as the organisms hide in the luminal debris and do not cause inflammatory changes. In the immunocompromised, collections of foamy histiocytes stuffing the lamina propria may represent *Mycobacterium avium-intracellulare* infection. However, the differential for stuffed macrophages also includes Whipple's disease, in which the macrophages are digesting Gram-positive rods and PAS-positive granules.

Neoplasms of the duodenum are unusual, but the most common of these are tubular adenomas (Figure 7.13), carcinoid tumors, and lymphoma (usually MALT type). Remember the intimate association of the duodenum to the pancreas and common bile duct; an adenocarcinoma found in duodenum may be originating in any of these organs.

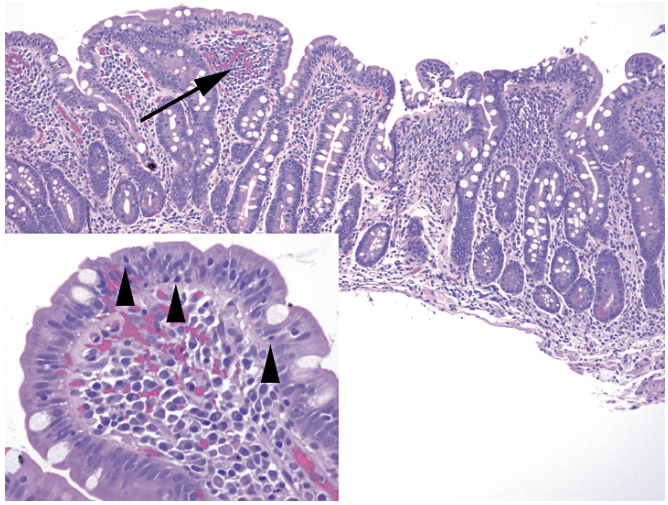

Figure 7.12. Celiac disease. The normal villi are blunted almost out of existence, with the duodenal mucosa resembling colon. There is chronic inflammation within the lamina propria (arrow). **Inset**: Increased numbers of intraepithelial lymphocytes are present (arrowheads).

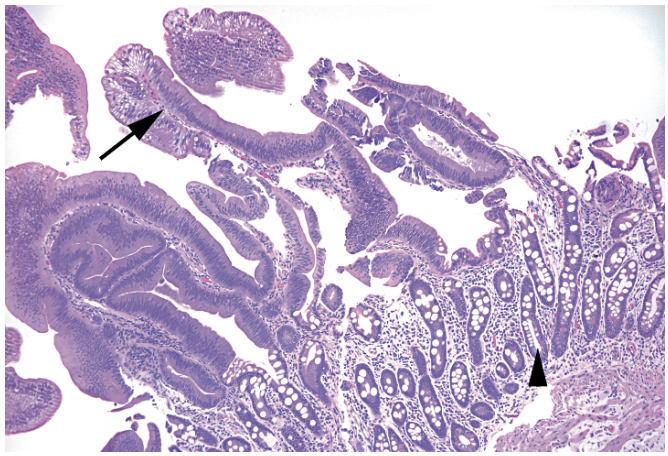

Figure 7.13. Duodenal adenoma. As in the colon, the tubular adenoma is characterized by low-grade dysplasia, showing crowded and elongated nuclei and loss of mucinous differentiation (arrow). Residual duodenal mucosa is seen underneath the adenoma (arrowhead).